Smoking and COVID-19: A Literature Review of Cohort Studies in Non-Chinese Population Settings

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ABSTRACT

BACKGROUND: Smoking history and its potential association with COVID-19 has attracted many researchers and the lay public alike. However, the studies published to date have several methodological limitations and are mainly from China. We set out to synthesize evidence on smoking and COVID-19 relationship drawn on cohort studies only which are published in non-Chinese population settings.

METHOD: A systematic literature search was undertaken drawn on predefined eligibility criteria and a comprehensive search strategy following the PRISMA guideline between January 2020 and August 2020, excluding preprints and gray literature. Three specific outcomes were examined: smoking history, SARS-CoV2 infection, and COVID-19 severity.

RESULTS: Of an eligible 40 full-text studies, 7 cohort studies outside of China were finally included in this literature review through independent reviewing. Four studies were from the UK, 2 from the United States, and 1 from Turkey. The sample size ranged from 200 to more than 5000 participants. The findings broadly point to 1 direction, a higher smoking prevalence and an increased risk of smoking history on both SARS-CoV2 infection and on COVID-19 severity.

CONCLUSION: A smoking history (either current or past) seems to negatively impact both SARS-CoV2 infection and COVID-19 severity. However, such an observation strengthens the argument to continue smoking cessation efforts both for individuals and for the general population health and well-being.

KEYWORDS: Smoking, COVID-19, severity, review: prospective

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Background

COVID-19 is now well-established as a global pandemic, contributing to thousands of deaths while SARS-CoV2 has infected millions of people across the globe.[1] As the disease evolves, it is important to explore the underlying determinants and the epidemiologic pattern of COVID-19. There has been an explosion of COVID-19-related publications, both as preprints and in peer-reviewed journals.[2] Therefore, it is important that evidence is synthesized on specific aspects of the epidemiology of COVID-19 for informing existing targeted public health strategies, which may have been impacted by the current pandemic. One such determinant is smoking, which causes approximately 8 million deaths each year across the globe before the pandemic.[3] Therefore, any potential association between smoking and COVID-19 would be a public health opportunity for tackling both the current pandemic and the tobacco epidemic toward population health and wellbeing.

Evidence to date on the potential association between smoking and COVID-19 is patchy and mixed.[4-6] In the early days of the pandemic, the evidence available to the global audience was mostly from China. The first systematic review on smoking and COVID-19 that was published in March 2020 included 5 studies – all from China.[7] Since then, several systematic reviews were published which included studies mainly from China but were mostly preprints.[5,6] A rapid "living" systematic review is also available – initially as a pre-print.[8] The Lancet has acknowledged the importance of preprints but reiterated quality.[9] A recent review of systematic reviews on smoking and COVID-19 has highlighted several methodological limitations of the systematic reviews published to date, such as small sample size, selection bias, and the lack of generalisability.[10] Therefore, we set out to address few of these potential gaps through a comprehensive literature review of smoking and COVID-19 including only cohort studies from settings outside of China which are peer-reviewed journal publications in English.

The overarching research question was "Are individuals with a smoking history at an increased risk of developing SARS-CoV2 infection, COVID-19 disease severity or mortality compared to those without a smoking history"?

Methods

Search strategy and selection criteria

A search was conducted in the PubMed database for studies published between January 1, 2020, to August 30, 2020. The Zotero 5.0.85 software was used to manage the selected studies. A comprehensive search was designed for the purpose of this study (Appendix 1). Only full-text studies were included in

Table 1. The inclusion and exclusion criteria.

INCLUSION
Only cohort studies conducted outside of China
Studies that described the epidemiological and/or clinical characteristics of the coronavirus infection
Studies that described the prevalence of smoking in the sample population, either as a whole or based on gender
Published peer-reviewed journals from December 2019 onwards
All in English language
EXCLUSION
Preprints, reviews (including systematic reviews), editorials and letters
Studies that provided no data about the smoking status of the sample populations affected by the coronavirus infections

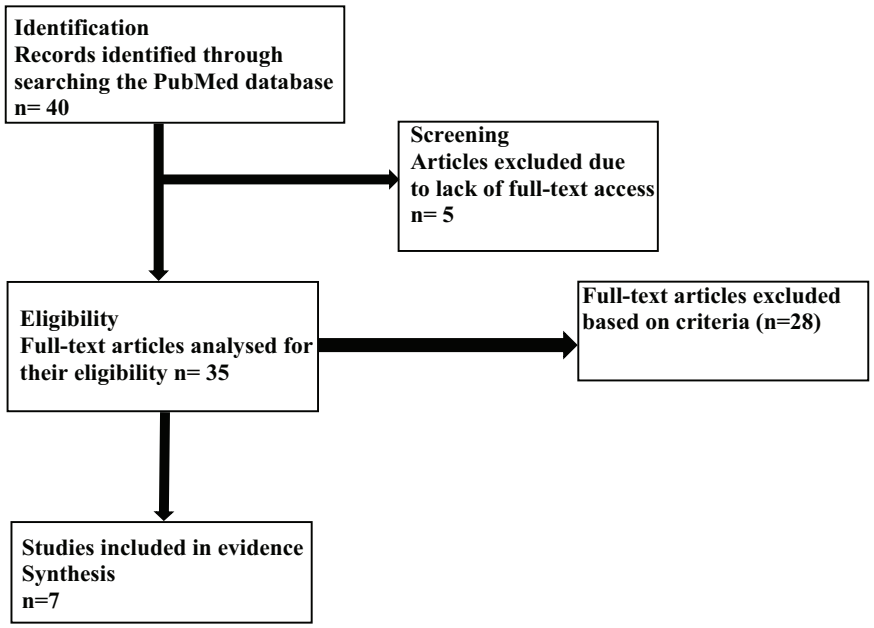

Figure 1. PRISMA flowchart.

the evidence synthesis. The studies identified by this search were further analyzed for their eligibility. Study characteristics of the selected studies (n = 8) are shown in Table 1. The PRISMA flowchart is available as Figure 1.

Narrative synthesis of evidence

The final number of cohort studies (both prospective and retrospective) included for narrative synthesis were 7 (all outside of China). Depending on the outcome of each study, the data presented in Table 2 reflects the heterogeneity of each study. The 3 outcomes presented for the exposure of interest (a smoking history – either a former smoker or a current smoker, as defined in each study) were: (1) smoking prevalence by subgroups; (2) severity of SARS-CoV2 infection (as demonstrated in each study of being hospitalized); (3) mortality (COVID-19-related deaths). If information on gender is available in any of the studies related to the above 3 outcomes, Table 2 also captures this. No quality appraisal was undertaken because of the nature of this literature review.

Results

A comprehensive search of PubMed between January 1, 2020 and August 30, 2020 yielded 40 peer-reviewed publications in non-Chinese population settings in alignment with our eligibility criteria of including only cohort studies. Of these 40 eligible, only 7 were finally included following full-text reviewing by 2 independent reviewers (AF & MN), and any conflicts were resolved by a third reviewer (ZK).

Two of these 7 studies were from the United States,[11,15] 1 from Turkey[14] and the remaining 4 were from the United Kingdom.[12-16,17] The sample populations in all these 7 studies were individuals who tested positive for COVID-19 from a target population. The population sample ranged from 200 (Bronx, US) to 502,640 (UK) patients. All the studies included were cohort studies (Table 2).

Table 2. Study characteristics.

TITLE	SETTING	POPULATION	STUDY-DESIGN AND TIME-HORIZON	OUTCOMES	SMOKING RATES BY OUTCOME
Jehi et al[11] Development and validation of a model for individualized prediction of hospitalization risk in 4536 patients with COVID-19	>220 outpatient locations and18 hospitals in Ohio and Florida	N=4536, All Covid positive patients, whether they were hospitalized or not, from across the Cleveland clinic health system. n=2852 tested before May 1 were included in the development cohort n=1684 tested May 1 and later comprised the validation cohort.	Retrospective cohort study of patients with COVID-19 applying a least absolute shrinkage and selection operator (LASSO) logistic regression algorithm, Between March 8, 2020 and June 5, 2020.	Disease severity: Development Cohort-Non-hospitalized=2270 Hospitalized=582 Validation Cohort-Non-hospitalized=1308 Hospitalized=376	Smoking history for hospitalized patients [n (%)]: Current smoker=37 (21.4)Former smoker=221 (25.6) *P*-value of association between smoking history and hospitalization ⩽.001
Lassale et al[12] Ethnic disparities in hospitalization for COVID-19 in England: The role of socioeconomic factors, mental health, and inflammatory and proinflammatory factors in a community –based cohort study	England	428,494 men and women (mean age 56.2years) from the UK Biobank study	Prospective cohort study, From 16th March to 26th April 2020	Disease severity: Non-hospitalized=427,594 Hospitalized=900	Smoking history for hospitalized patients (%): Current smokers=11.4Past smokers=41.9 *P*-value of association between smoking history and hospitalization ⩽0.001
McQueenie et al[13] Multimorbidity, polypharmacy, and COVID-19 infection within the UK Biobank cohort	England, Scotland and Wales	428,199 participants aged between 37 and 73years old were recruited from the UK Biobank	A longitudinal population-based cohort study from 2006 to 2010	Disease vulnerability: Participants who tested positive for COVID-19 were older and more likely to be male, and current/former smokers, compared to those who did not have a positive COVID-19 test	Smoking history for patients testing positive for COVID19; Non-smokers: 49% (n=642) tested positiveCurrent/ previous smoker: 51% (n=669) tested positive.
Şenkal et al[14] Association between chronic ACE inhibitor exposure and decreased odds of severe disease in patients with COVID-19	Istanbul	611 patients (age ⩾18years) with COVID-19 admitted to the İstanbul Faculty of Medicine Corona Center. Included were 363 males and 248 females with an average age of 57 ± 15years.	A retrospective cohort study carried out between March 9th and May 11th, 2020	Disease severity: Non-Hospitized: N=165 (27%). Hospitalized: N=446 (73%)	Smoking history in non-severe patients: 11% (n=48).Smoking history in severe patients: 13% (n=21). Smoking being a predictor of severe disease had an odds ratio higher than 1.
Palaiodimos et al[15] Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York	The Bronx, New York	200 patients were included. 102 females, 98 males with the median age of 64years.	A retrospective cohort study of the first 200 patients who presented to the emergency room (ER) and were admitted to the inpatient medicine service or the intensive care unit (ICU) with laboratory-confirmed COVID-19.	The in-hospital mortality was 24% with severe obesity (BMI ⩾35kg/ m^2), increasing age, and male sex linked to more severe outcomes.	Smoking was found to be a significant predictor of increasing oxygen requirements during hospitalization.
Raisi-Estabragh et al,[16] Renin-Angiotensin-Aldosterone System Blockers Are Not Associated With Coronavirus Disease 2019 (COVID-19) Hospitalization: Study of 1439 UK Biobank Cases	England	7099 participants from the UK Biobank who had been tested for COVID-19 in hospital.1439 tested positive and 5660 tested negative.	Prospective cohort study, From 16th March to 14th of June, 2020	It was predominantly males who tested positive for COVID-19 (52.9% vs 45.5%).	Smoking association to a positive COVID19 test: Non-smoker: Of 5660 non-smokers, 51.8% (N=2931) tested positive for COVID19.Current/former smoker: Of 1439 smokers, 50.9% (n=1439) tested positive.The odds ratio by predictor found smoking to have a statistical significance when testing positive for COVID19.
Woolford et al,[17] COVID-19 and associations with frailty and multimorbidity: a prospective analysis of UK Biobank participants	England, Scotland and Wales	502,640 participants aged 40 to 69years were recruited for COVID-19 (positive=1326, negative=3184).	A prospective community-based cohort analysis from 16th March 2020 to 1st June, 2020	no differences for frailty status or number of morbidities when com-paring those who tested positive for COVID-19 and those who tested negative, Suggesting associations compared to background population influence disease progression for admission to hospital rather than COVID19	Association between smoking and COVID19.Non-smokers: 49% (643) of non-smokers were positive for COVID19 with 48.3% (n=1526) of non-smokers testing negative.Current/ former smokers: 50.52% tested positive with 51.35% testing negative.

The findings of this review are summarized below. We also report adjusted odds ratios where available.

Jehi et al[11] in the US of 4536 patients reported significant higher smoking rates ($P < .001$) among those hospitalized (n = 958) across 2 cohorts (development and validation) – 8.6% were current smokers and 36.4% were former smokers compared to 6.9% and 26.3%, respectively, among those who were not hospitalized.

Lassele et al[12] in England studying 428,494 individuals using the UK Biobank study reported a similar trend as Jehi et al study: significantly higher smoking rates among those hospitalized (n = 900) compared to those not hospitalized (n = 427,594), 41.9% former smokers and 11.4% current smokers as against 34.6% former and 10% current smokers, respectively. The same study reported significantly higher odds of hospitalizations among former and current smokers compared to non-smokers (1.30; 95% CI:1.10-1.55 and 1.25; 95% CI: 0.96-1.62), respectively, following multivariable regression.

Another UK Biobank Study (McQueenie et al[13]) reported smoking prevalence among those who tested COVID-19 positive (n = 1324) and those who tested negative or were not tested (n = 426,875), 51% were ever smokers (current and former combined) as against 44.6% among those who were negative, respectively. The same study also reported that ever-smokers had an increased risk of testing COVID-19 positive in individuals with no multimorbidity (1.26; 95% CI: 1.02-1.57) in the multivariable analysis.

A retrospective cohort study in Istanbul,[14] Turkey of 611 in-patents (Şenkal et al) reported a higher smoking rate (13%) among those defined as severe as compared to those who were categorized as "non-severe" (11%), and this was not significant ($P = 0.56$).

The smallest study (Palaiodimos et al[15]) in this review (n = 200) of all COVID-19 in-patients from Bronx, New York reported an ever-smoking rate of 32.5%, which is certainly higher than the smoking rate in general population of New York City. The same study reported in the univariate analyses that ever-smokers had higher odds of in-patient mortality (1.19; 95% CI: 0.60-2.36) but in multivariable analyses ever-smoking was found to be protective of in-patient mortality (0.83; 95% CI: 0.37-1.87) albeit not a significant association. However, this study showed that COVID-19 in-patients who were ever-smoking had an increased odds of oxygen requirements in a multivariable analysis (2.10; 95% CI:1.07-4.10).

Another UK Biobank study[16] of 7099 participants (Raisi-Estabragh et al) reported that 1439 tested COVID-19 positive. Of these, 50.9% were ever-smokers compared to 51.8% ever-smokers among those who tested negative. The same study reported a higher odds (1.26; 95% CI: 1.13, 1.40) of testing COVID-19 positive among ever-smokers when compared to those who were COVID-19 test negative and were not tested (n = 494,838) in the multivariable analyses, but did not reach statistical significance when the untested populations were excluded from the model (1.02; 95% CI: 0.90, 1.15).

The largest study[17] in this review included 502,640 participants from the UK Biobank (Woolford et al). 4510 of the participants were tested for COVID-19 and 1326 tested positive. 40% of those who tested positive were former smokers as opposed to 37.8% among those who tested negative. However, 11% were currently smoking among those who tested positive as against 14% among those who tested negative. All these findings were significant when compared with the background population ($P < .001$).

In summary, all the 7 studies included show an apparent higher risk of COVID-19 among the ever-smoking population, and more pronounced among former smokers.

Discussion

This review of cohort studies outside of China examining the relationship of smoking and COVID-19 is an explorative narrative synthesis following a systematic approach, with predefined eligibility criteria and search strategy. The conclusion across all these 7 studies are broadly in the same direction, pointing toward a potential harmful effect of smoking on COVID-19 severity and being more susceptible to contracting SARS-CoV-2 infection. However, the observation of an increased risk of COVID-19 among former smokers is intriguing. This observation is consistent across several studies both included in this review and few of those which did not qualify for this review.[18,19] This observation needs careful attention and deeper exploration, especially related to timing of quitting smoking, because it is probable that those smokers with morbid conditions could have quit smoking once they were diagnosed with COVID-19.

Some of the strengths of this review include the robustness of eligibility criteria of not including pre-prints and to include only cohort studies. Pre-defined eligibility criteria and a comprehensive search strategy also lends support to the rigor of this review. A systematic approach to include studies outside of Chinese population settings may add to the strength of this review for several reasons. First, a systematic review of initial 5 Chinese studies have already been published in March 2020.[7] Second, several systematic reviews post this first systematic review have also been published, majority of these reviews did include studies from China and were preprints.[5,6] Third, the evolution and the epidemiology of COVID-19 adds to the complexity of reproducibility – and this was evident from the studies published in the initial stage of the pandemic which were mainly from Chinese hospitals and had small population sample.[7] Therefore, these initial studies from China and elsewhere were either cross-sectional or hospital-based and were methodologically weak: selection bias, the lack of generalizability, confounding, and relatively of small sample size. We aimed to address these limitations in our current review by including only cohort studies.

Our review has some methodological limitations. We did not undertake a systematic review or a meta-analysis because of the heterogeneity of the papers. Our limit to only published peer-reviewed literature instead of including gray literature may have influenced our search strategy. We searched only 1 database, the PubMed, which is otherwise considered one of the most comprehensive peer-reviewed medical literature databases to date. Finally, not all studies included in this review had all the parameters that we were interested in examining. Examples include, self-reported smoking history (some had no specific distinction between current and former smokers), the lack of adjusted estimates for the specific outcomes of interest, no gender breakdowns, no unified operational definition of "severity" of COVID-19 across the studies reviewed, and the inability to capture "infectiousness" of SARS-CoV2 owing to the nature of the currently COVID-19 diagnostic tests widely employed across these countries. All these methodologically inherent limitations need to be addressed in future research to infer a more concrete conclusion on smoking and COVID-19 progression.

Furthermore, the epidemiology and the natural history of this pandemic is evolving. Therefore, it would be premature to speculate on the probable causal mechanism of this observation between a smoking history and SARS-CoV2 infection and its sequelae. Several potential mechanisms have been postulated, especially in relation to upregulation of ACE2 receptors and smoking, and also the role of nicotine on anti-cholinergic pathway.[20,21] However, the totality of evidence in terms of the global tobacco epidemic remains unaltered, smoking kills 8 million individuals every year globally, and any additional attribution of smoking to SARS-CoV2 infection quite naturally will increase the burden on the current pandemic. Therefore, smoking cessation and avoidance of secondhand smoke exposure must remain the cornerstone of population health and well-being, despite the lingering uncertainty.

Ethical Considerations

No personal data were used, therefore no ethical approval was sought

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Appendix 1. The PICO.

POPULATION	ALL COVID-19 CASES
Intervention/Exposures	Smoking history (current/former smokers)
Comparison	Non-smokers
Outcomes	Smoking prevalence; SARSCoV2 infection; Severity & mortality of COVID-19 (hospitalizations/deaths)

Appendix 2. Detailed search strategy in PubMed using Boolean operators.

SEARCH NUMBER	QUERY	SEARCH DETAILS	RESULTS
3	(((smoking) AND (Covid-19)) AND (severity)) AND (sex)	((((((((((“smoke”[MeSH Terms] OR “smoke”[All Fields]) OR “smoke s”[All Fields]) OR “smoked”[All Fields]) OR “smokes”[All Fields]) OR “smoking”[MeSH Terms]) OR “smoking”[All Fields]) OR “smokings”[All Fields]) OR “smoking s”[All Fields]) AND (((((((“covid 19”[All Fields] OR “covid 2019”[All Fields]) OR “severe acute respiratory syndrome coronavirus 2”[Supplementary Concept]) OR “severe acute respiratory syndrome coronavirus 2”[All Fields]) OR “2019 ncov”[All Fields]) OR “sars cov 2”[All Fields]) OR “2019ncov”[All Fields]) OR ((“wuhan”[All Fields] AND (“coronavirus”[MeSH Terms] OR “coronavirus”[All Fields])) AND (2019/12/1:2019/12/31[Date - Publication] OR 2020/1/1:2020/12/31[Date - Publication]))))) AND ((((((((“sever”[All Fields] OR “severe”[All Fields]) OR “severed”[All Fields]) OR “severely”[All Fields]) OR “severer”[All Fields]) OR “severes”[All Fields]) OR “severing”[All Fields]) OR “severities”[All Fields]) OR “severity”[All Fields]) OR “severs”[All Fields])) AND (“sex”[MeSH Terms] OR “sex”[All Fields])	40
2	((smoking) AND (Covid-19)) AND (severity)	((((((((((“smoke”[MeSH Terms] OR “smoke”[All Fields]) OR “smoke s”[All Fields]) OR “smoked”[All Fields]) OR “smokes”[All Fields]) OR “smoking”[MeSH Terms]) OR “smoking”[All Fields]) OR “smokings”[All Fields]) OR “smoking s”[All Fields]) AND (((((((“covid 19”[All Fields] OR “covid 2019”[All Fields]) OR “severe acute respiratory syndrome coronavirus 2”[Supplementary Concept]) OR “severe acute respiratory syndrome coronavirus 2”[All Fields]) OR “2019 ncov”[All Fields]) OR “sars cov 2”[All Fields]) OR “2019ncov”[All Fields]) OR ((“wuhan”[All Fields] AND (“coronavirus”[MeSH Terms] OR “coronavirus”[All Fields])) AND (2019/12/1:2019/12/31[Date - Publication] OR 2020/1/1:2020/12/31[Date - Publication]))))) AND ((((((((“sever”[All Fields] OR “severe”[All Fields]) OR “severed”[All Fields]) OR “severely”[All Fields]) OR “severer”[All Fields]) OR “severes”[All Fields]) OR “severing”[All Fields]) OR “severities”[All Fields]) OR “severity”[All Fields]) OR “severs”[All Fields])	214
1	(smoking) AND (Covid-19)	((((((((“smoke”[MeSH Terms] OR “smoke”[All Fields]) OR “smoke s”[All Fields]) OR “smoked”[All Fields]) OR “smokes”[All Fields]) OR “smoking”[MeSH Terms]) OR “smoking”[All Fields]) OR “smokings”[All Fields]) OR “smoking s”[All Fields]) AND (((((((“covid 19”[All Fields] OR “covid 2019”[All Fields]) OR “severe acute respiratory syndrome coronavirus 2”[Supplementary Concept]) OR “severe acute respiratory syndrome coronavirus 2”[All Fields]) OR “2019 ncov”[All Fields]) OR “sars cov 2”[All Fields]) OR “2019ncov”[All Fields]) OR ((“wuhan”[All Fields] AND (“coronavirus”[MeSH Terms] OR “coronavirus”[All Fields])) AND (2019/12/1:2019/12/31[Date - Publication] OR 2020/1/1:2020/12/31[Date - Publication]))))	327